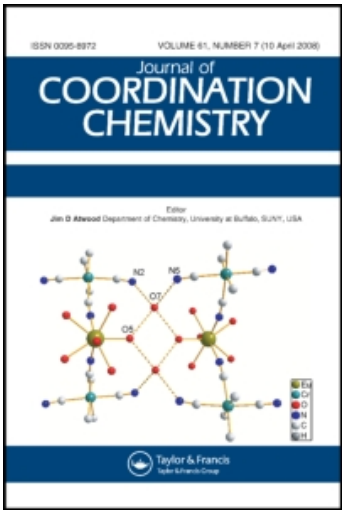

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Biomimetic Membrane Transport *via* Designed Macrocyclic Host Molecules

Hiroshi Tsukube[a]
[a] Department of Chemistry, College of Liberal Arts and Science, Okayama University, Okayama, Japan

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BIOMIMETIC MEMBRANE TRANSPORT *VIA* DESIGNED MACROCYCLIC HOST MOLECULES

HIROSHI TSUKUBE

Department of Chemistry, College of Liberal Arts and Science, Okayama University, Okayama 700, Japan

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Biomimetic approaches to naturally occurring ion transport were discussed. Selective transport systems of alkali, alkaline earth, heavy, and transition metal cations as well as organic cations and anions were successfully constructed by using "synthetic" ionophores. They were designed by considering (i) sizes of their molecular cavities for guest-binding; (ii) natures of their binding sites; and (iii) their three-dimensional ligand topologies. Their synthetic strategies, guest-binding and transport abilities, and biological significance were mainly described.

Keywords: membrane transport, crown ether, ionophore, polyamine macrocycle, armed macrocycle, host-guest chemistry

1. INTRODUCTION

Since the antibiotic "nigericin" was isolated in 1951 as the first representative of the biological ion-carriers, so-called "ionophores" have attracted wide attention and numerous investigations.[1] They are known to specifically transport biologically active guest species across a membrane. For example, valinomycin transports K^+ ion with a ten-thousand times greater efficiency than that of Na^+ ion, while monensin selectively transports Na^+ ion against its concentration gradient. Their molecular structures, ion binding and transport abilities, physiological activities, and other chemical properties have been extensively studied, and their molecular recognition and transport functionalities should be outlined.

Molecular recognition and transport phenomena are also important subjects of current chemistry, especially host-guest chemistry and biomimetic chemistry. Since Pedersen discovered crown ether compounds in 1967, a variety of macrocyclic host molecules have been prepared and widely applied in chemistry, industry, and related fields.[2] Their most striking functionalities are specific complexations and solubilizations of inorganic metal salts. Since these functionalities are closely similar to those observed with biological ionophores, naturally occurring ion transport phenomena are successfully mimicked by using these synthetic materials.[3,4] Therefore, we expect that such approaches can open new aspects of membrane biology and also develop a variety of applications. Concentration of rare or toxic metals, optical resolution of racemates, separation of radioisotopes, and related processes may be possible.

This review describes our original biomimetic approaches to naturally occurring ion transport, especially focusing on molecular design of synthetic "ionophores". Their synthetic strategies and chemical functionalities are mainly discussed, together with a brief background of membrane transport phenomena.

2. GUIDELINES FOR DESIGN OF SYNTHETIC IONOPHORES AND THEIR MEMBRANE SYSTEMS

The molecular design of synthetic ionophores specific for a given guest species can be generally achieved by mimicking biological ionophores. Crystallographic studies of biological ionophores and their metal complexes have revealed that they have several features in common as potential host molecules:

(i) They form three dimensional inclusion complexes specifically with guest species;

(ii) They contain suitable hydrophilic and lipophilic units, and bind polar guest species and solubilize them into non-polar membranes;

(iii) Both complexation and decomplexation processes are highly dynamic, leading to effective transport.

If we could prepare artificial host molecules which met these requirements, they would be expected to act as "synthetic ionophores" showing excellent ion transport abilities, as observed in the biological systems.

Macrocyclic crown ethers are promising candidates for specific cation transport ionophores. In 1973, Cussler *et al.* presented the first example of biomimetic membrane transport, in which the macrocyclic crown compound, dibenzo-18-crown-6, mediated artificial transport of metal cations.[5] It showed interesting transport abilities for alkali and alkaline metal cations through a bulk liquid membrane. As shown in Figure 1, K^+ ion was selectively bound and specifically transported by the crown ether, while Na^+, Li^+, and Cs^+ cations were slightly transported. Since an effective and selective transport was realized by such a simple synthetic material, further extensions along this line may provide new insight into biological membrane transport as well as potential applications in various chemical processes.

Host-guest complexation is based on several different types of molecular interactions including electrostatic force, hydrogen bonding, charge-transfer force, hydrophobic interaction, and metal-coordination.[6] In naturally occurring enzyme-substrate, antigen-antibody, and other molecular recognition systems, these molecular interactions act cooperatively and complementarily, and offer precise molecular recognition. Since synthetic host molecules capable of guest-binding have advantages of facile synthesis and of versatility of molecular structures, the appropriate choice of guest binding sites may lead to a specific host molecule for a given guest species "at will".

Recently we designed and synthesized several types of macrocyclic host molecules showing characteristic guest-binding and transport abilities by considering

(A) sizes of their molecular cavities for guest-binding,

(B) nature of their donor sites,

(C) their three-dimensional ligand topologies.

Macrocyclic host molecules possessing a well-defined molecular cavity distinguish guest species *via* inclusion complexation, and adjusting size-fitting between the host cavity and the guest species dramatically enhances guest-binding specificity. The nature of the donor site in the macrocyclic system is also an essential factor in determining guest-binding properties. For example, soft sulfur atom-containing macrocycles form very stable complexes with soft heavy metal cations but less stable complexes with hard alkali metal cations. Hence, the distribution of characteristic donor sites will display a wide variety of guest-binding characteristics.[7] Further, precise host-guest complexation requires highly structural complementarity between host

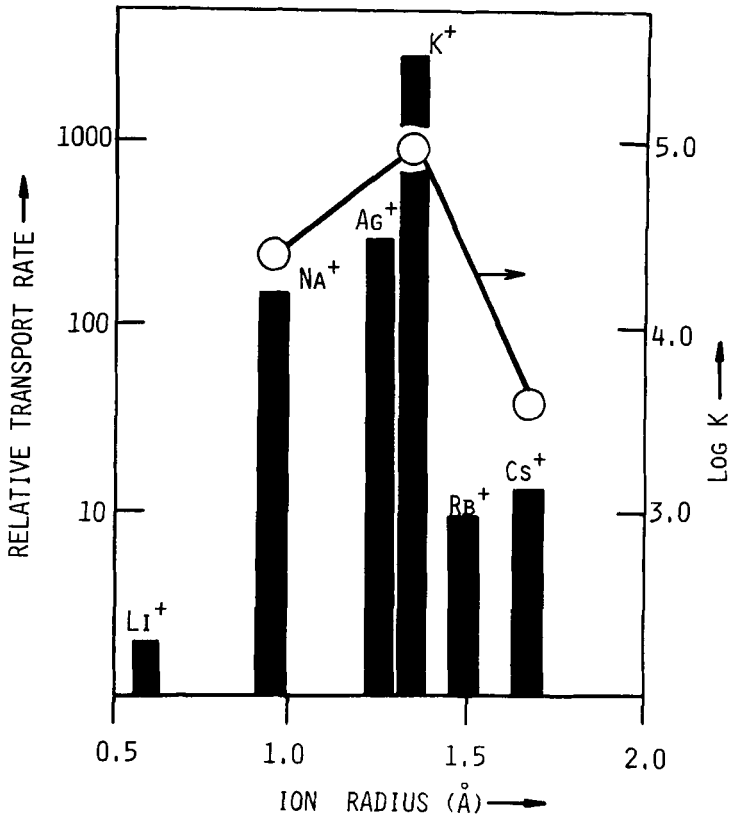


FIGURE 1 Transport rates and complexation constants of dibenzo-18-crown-6 for a series of alkali metal cations.

and guest species. An optimal three dimensional arrangement of donor sites in the macrocyclic host cavity makes it possible to recognize both size and shape of a given guest species.

Our newly developed ionophores have wide variations in their structures and offer characteristic membrane transport functionalities. Although naturally occurring ionophores transport limited kinds of biological species such as Na^+, K^+, and catecholamine cations, artificial transport of alkali, alkaline earth, heavy, and transition metal cations as well as organic cations and anions was successfully mediated by our designed ionophores. Their synthesis, guest-binding and transport properties, and biological significance are presented in the following sections.

3. EXPERIMENTAL SETUP FOR MEMBRANE TRANSPORT

Several membrane systems have been constructed for ion transport experiments: polymer film membranes, bulk liquid membranes, vesicles, and others. A bulk liquid membrane system was usually employed, because it promised reproducible experimental data without difficulties. Typically, the transport experiments were performed at ambient temperature in a U-tube glass cell as shown in Figure 2. The lipophilic ionophore in CH_2Cl_2, $CHCl_3$, or other organic media (Membrane) was placed in

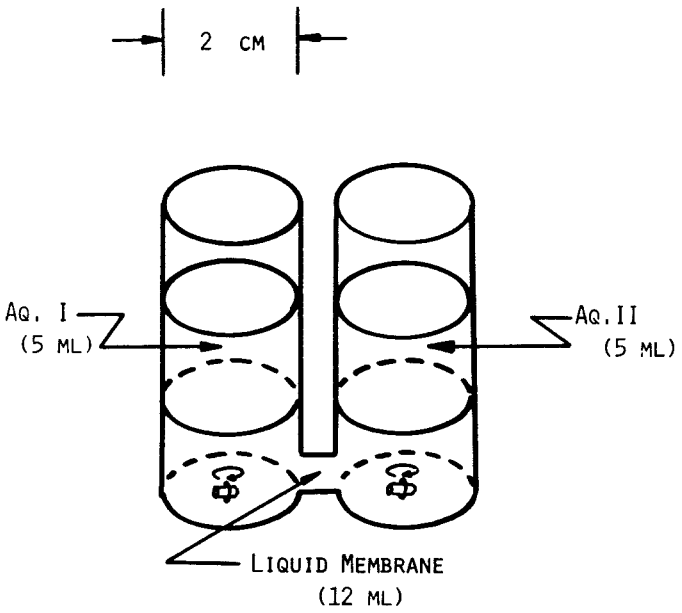


FIGURE 2 Typical experimental setup for membrane transport

the bottom of the U-tube. Two aqueous phases (Aq. I and II), source and receiving phases, were placed in the arms of the U-tube, floating on the organic membrane phase. The membrane phase was constantly stirred by a magnetic stirrer (ca. 100 rpm). The transported amounts of guest species were determined from the concentrations of guest species in the receiving aqueous phase. Ion-selective electrode, colorimetric, and spectroscopic methods were available for determinations of guest species. Reproducibility of the data was confirmed as 15% or better. We also prepared polyvinylchloride membranes and polymer-supported liquid membranes for several ionophores, and obtained results parallel to those observed with corresponding bulk liquid membrane systems.

4. SYNTHETIC IONOPHORES SHOWING CATION-BINDING AND TRANSPORT FUNCTIONALITIES

4.1. *Membrane System for Cation Transport*

Cationic guest species including inorganic and organic substrates are transported by two different types of ionophores: neutral host molecules transport cationic guests together with symport anions and anion-bearing host molecules carry cationic guests *via* a cation/cation exchange mechanism.

When a guest salt, M^+X^-, is transported by neutral ionophores such as synthetic crown ether **1**, biological valinomycin **2**, and nonactin **3**, four elemental processes are involved (Figure 3, symport):

(i) At the interface of Aq. I/Membrane, M^+ and X^- are complexed with the neutral ionophore;

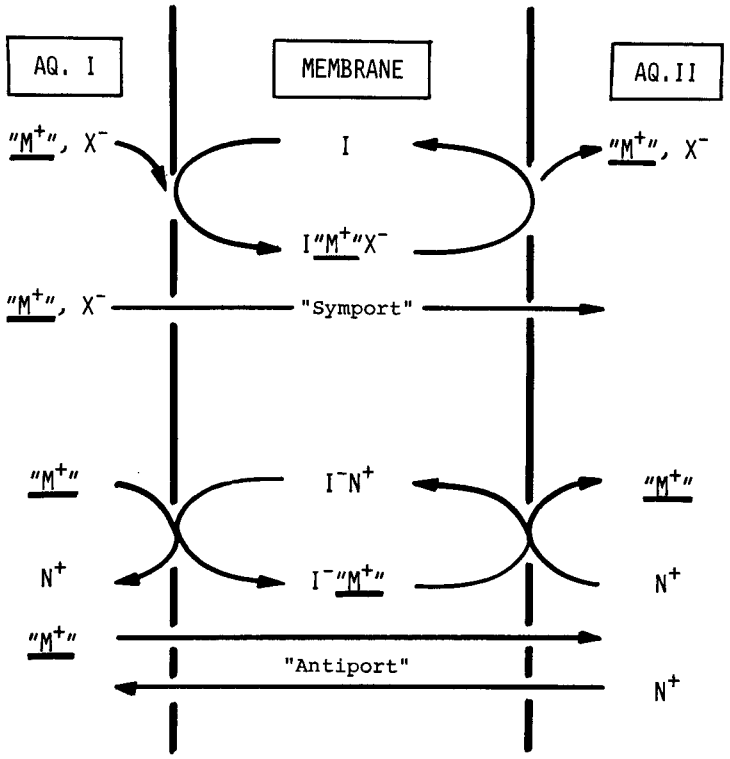


FIGURE 3 Two typical membrane systems for cation transport: "symport" and "antiport". I or I^-: ionophore; M^+: guest cation; X^-: symport anion; N^+: antiport cation.

(ii) The resulting lipophilic complex diffuses across the Membrane;

(iii) The release of the guest salt occurs at the interface of Membrane/Aq. II;

(iv) The freed neutral ionophore diffuses back across the Membrane.

In this symport system, guest M^+ and symport X^- ions are effectively transported through the Membrane in the same direction.

Anion-bearing ionophore molecules such as biological monensin **4** and lasalocid A **5** show somewhat different transport mechanisms (Figure 3, antiport):

(i) At the interface of Aq. I/Membrane, the anion-bearing ionophore forms an electrically neutral complex with the guest M^+ ion;

(ii) The resulting lipophilic ion-pair complex diffuses across the Membrane;

(iii) Rapid cation exchange reaction with antiport N^+ ion releases guest M^+ ion;

(iv) The ionophore $\cdot N^+$ complex difuses back across the Membrane.

As a result, guest M^+ and antiport N^+ ions are transported through the Membrane in opposite directions.

Two characteristics of these membrane transport systems deserve special mention. First, a selective transport system can be constructed by using an ionophore which shows guest selectivity either in the complexation or in the decomplexation process. Second, apparently active transport, so-called "up-hill" transport, is also possible.

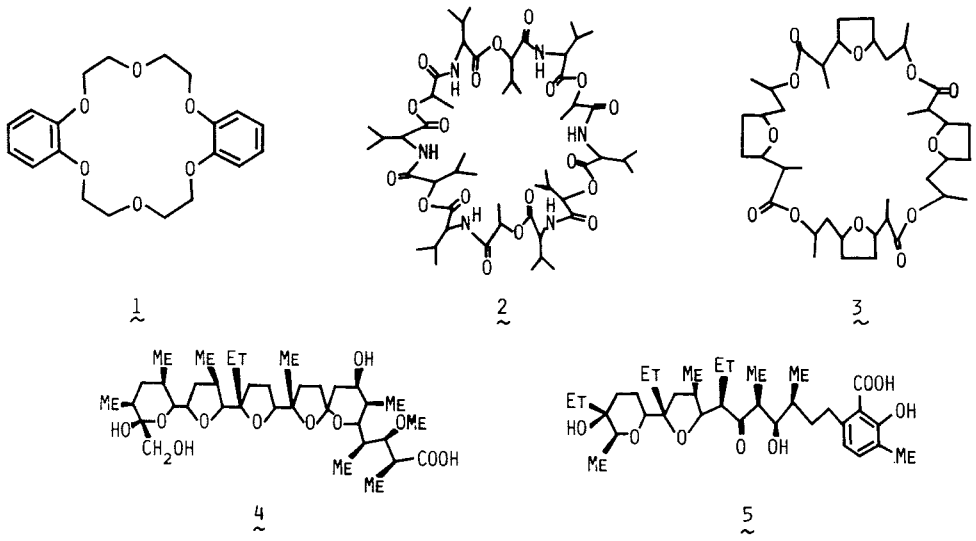


FIGURE 4

Since the flux of guest M^+ ion clearly couples with the flux of X^- or N^+ ion, the concentration gradient of X^- or N^+ ions across a Membrane can drive both down-hill and up-hill transport of guest M^+ ion.

Here we present three different types of synthetic neutral ionophores, which are classified as "podands", "coronands", and "podandocoronands" according to the ligand dimensions (Figure 5).[7] "Coronands" are multidentate monocyclic ligands with several types of donor atoms, while "podands" are corresponding acyclic multidentate ligands. "Podandocoronands" have unique ligand geometries between those of monocyclic coronands and bicyclic cryptands. Furthermore, we describe new biomimetic membrane transport, in which anion-bearing ionophores are involved. In particular, some biological ionophores bearing anionic moieties were found to show new transport functionalities for unnatural but important guest cations.

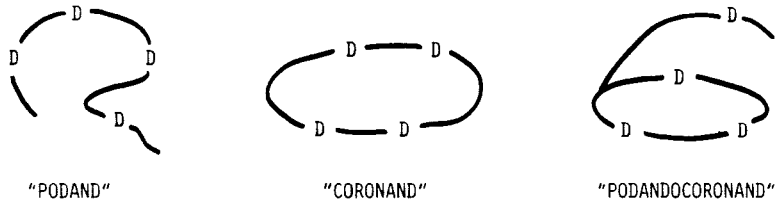


FIGURE 5 Typical structural dimensions of synthetic ionophores: "Podands", "Coronands", and "Podandocoronands".

4.2. *Polyamine and Polyamide Macrocycles as New "Coronand" Type Ionophores*

Since the discovery of crown ethers, efforts have continued to synthesize "coronand" type compounds with different numbers, distributions, and types of donor heteroatoms.[8] We prepared a new series of "coronand" type ionophores having amino-nitrogen atoms or amide-groups as donor sites (Figure 6). As is well-known, several

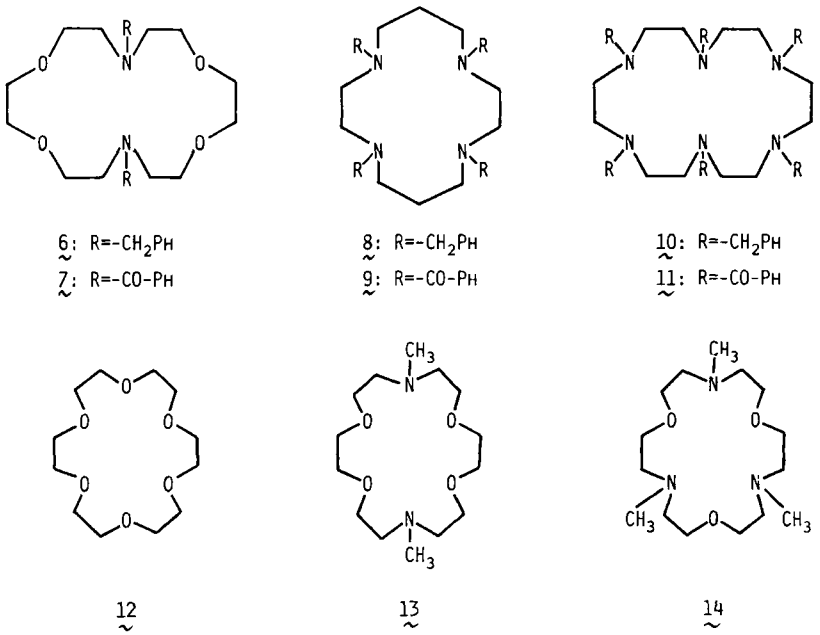


FIGURE 6

complicated carrier proteins are involved in biological transport of amino acids and other organic substrates. The proteins recognize and bind their guest species *via* specific interactions with the amino- and amide-residues in the proteins. Synthetic macrocyclic polyamine and polyamide compounds **6–11** have similar binding sites in the macrocyclic systems and may form complexes specifically with organic cations, especially ammonium cations of amino acid derivatives. The interactions involved are:

(i) charge-dipole attraction between guest ammonium cations and electro-negative donor atoms in the macrocycle;

(ii) hydrogen bonding from hydrogen atoms of guest ammonium cations to the amino-nitrogen atoms or amide-oxygen atoms;

(iii) hydrophobic interaction between alkyl- or aryl-substituents on guest ammonium cation and aromatic residues of the macrocycles.

Recently several polyamine macrocycles have been prepared representing a new class of host molecules capable of cation-binding. Lehn *et al.* systematically studied complexations between primary ammonium cations and N, O-mixed donor crown ethers **12–14** in homogeneous solutions.[9] The significance of hydrogen bonding between the macrocyclic ring nitrogen atoms and the guest ammonium cation was emphasized. Among a series of 18-membered crown ethers, N_3, O_3-mixed donor crown ether **14** was found to bind primary ammonium cations *via* three tight hydrogen bonds more strongly than O_6- and N_2, O_4-donor crown ethers **12** and **13**. Kimura *et al.* also proposed similar hydrogen bonding between macrocyclic polyamine nitrogen atoms and catechol moieties.[10] Although no application of polyamine macrocycles to membrane transport has been reported, polyamine compounds, if lipophilic groups are attached, would become promising candidates for novel cation transport ionophores.[11]

Tsukube *et al.* examined cation-binding properties of a series of lipophilic polyamine and polyamide macrocycles **6**–**11**.[12,13] Table I indicates liquid-liquid extraction profiles of 18-membered polyamine **10**, polyamide **11**, and polyether **1** macrocycles for amino acid ester salts. Among them, macrocycle **10** having six amino-nitrogen atoms showed selective extraction abilities for ammonium cations of amino acid esters, while alkali and alkaline earth ions were hardly extracted under the conditions employed. Interestingly, the cation-extraction abilities of **10** were much higher than those of the corresponding polyamide **11** and polyether **1**. Polyamine nitrogen atoms could act as strong and selective binding sites for organic ammonium cations. In other words, the nature of the donor sites in the macrocyclic ring system significantly controlled the selectivity and efficiency in the cation-extraction process.

Table I also reveals that the extraction abilities were markedly enhanced by adding the hydrophobic ClO_4^- anion. In particular, $HClO_4$ salt of phenylalanine ester was extracted semiquantitatively by hexa-amine macrocycle **10**. Hexa-amide **11** and hexa-ether **1** showed parallel enhanced cation extraction properties, but their extractabilities were relatively low even in the presence of the ClO_4^- anion. Spectroscopic study clearly indicated that polyamine macrocycles tightly bind guest ammonium cations in a different manner from the corresponding polyamide and polyether macrocycles. When the phenylazoaniline · HCl salt was employed as a probe, its absorption spectrum was drastically changed in the presence of polyamine macrocycles, while no spectral change was observed in the presence of polyamide and polyether macrocycles. Probably, the primary ammonium guest cation is tightly bound to the polyamine macrocycle *via* strong hydrogen bonds between $N^+H....N$, and hydrophobic anions such as ClO_4^- promote solubility of the guest salts in the organic media.

Characteristic cation-binding properties of polyamine and polyamide macrocycles led to new cation transport phenomena which were not attained by using common polyether macrocycles (Figure 7).[12,13] Cation transport experiments were carried out in $CHCl_3$ liquid membrane systems as shown in Figure 3. Membrane transport, in general, is composed of a series of complicated elemental processes, but some of them are similar to those of cation-extraction: the macrocycle extracts the guest cation salt from the source aqueous phase (Ag. I), carries it through the Membrane, and then releases it to the receiving aqueous phase (Aq. II).

Polyamine and polyamide macrocycles **8**–**11** specifically discriminated organic ammonium cations from a variety of inorganic cations in the transport process. They effectively transported several amino acid ester salts, though Na^+, K^+, and NH_4^+ ions were hardly transported. On the other hand, polyether macrocycle **1** showed

TABLE I
Cation-extraction properties of coronand type ionophores

Coronand	Extraction Percentage (%)[a]			
	GlyOEt		PheOEt	
	HCl salt	$HClO_4$ salt	HCl salt	$HClO_4$ salt
1	2.0	2.0	11.5	13.2
10	2.0	7.5	16.0	61.2
11	2.0	2.8	9.0	9.3

[a][Amino acid ester extracted into $CHCl_3$]/[Amino acid ester added initially] × 100.

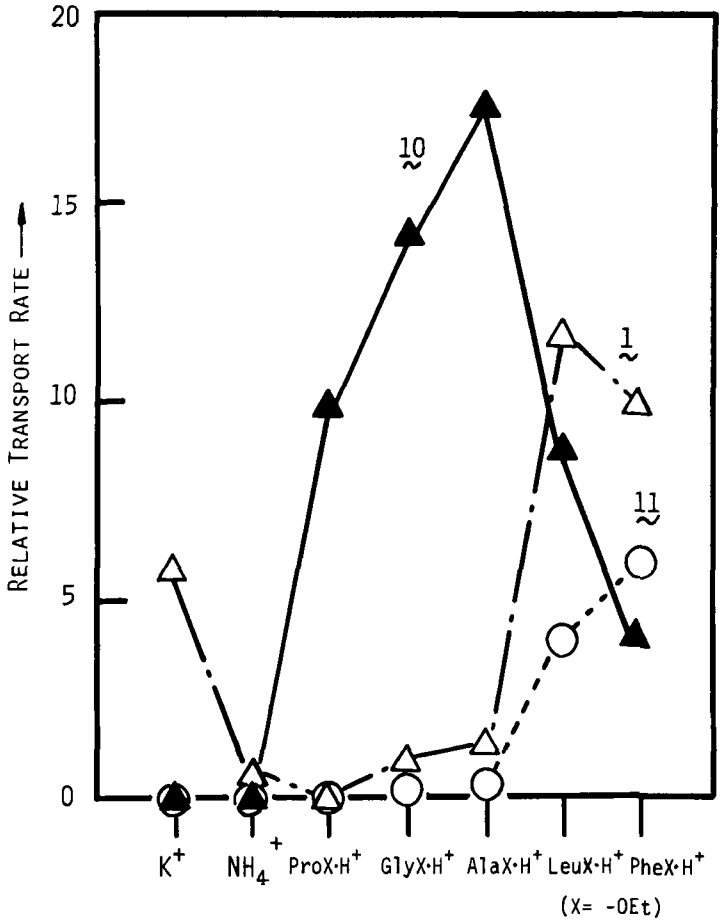


FIGURE 7 Cation transport profiles of "Coronand" type ionophores **1**, **10**, and **11**.

high transport efficiencies both for organic and inorganic guest cations. As its cation-binding and transport properties were significantly controlled by the "ion-cavity" size concept,[7] crown ether type ionophores could not distinguish cations having similar ion sizes such as $R-NH_3^+$ and K^+ cations. Introduction of new binding sites into the macrocyclic ionophore provided new site-controlled cation-binding and transport phenomena. Detailed transport selectivities for a series of amino acid ester salts could be adjusted by appropriate choice of macrocyclic host molecules. Polyamine macrocycles **8** and **10** transported glycine and alanine ester salts more effectively than phenylalanine and tryptophane ester salts, while polyamides **9** and **11** showed higher transport rates for phenylalanine and tryptophane derivatives than those for glycine and alanine derivatives. Liquid-liquid extraction experiments supported the idea that both transport systems have different rate-determining steps. Since polyamine extracted hydrophobic phenylalanine salts much more effectively than hydrophilic glycine esters, the releasing process of guest cation from the membrane into the receiving phase (Aq. II) determined the overall transport rate. In marked contrast, transport trends of polyamide macrocycles were parallel to those

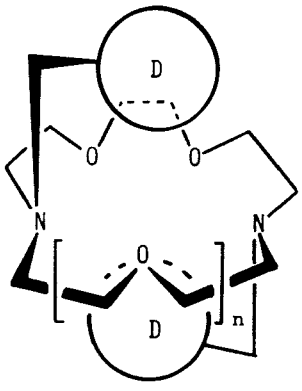
of the extraction experiments, indicating that an extraction process is essentially involved. Therefore, the control of transport efficiency and selectivity was possible by altering the donor sites in the macrocyclic ionophores.

Ring-size of the polyamine or polyamide macrocycle was an essential factor in determining the transport rate, as frequently reported in crown ether type ionophore systems. Macrocyclic hexa-amine **10** mediated transport of amino acid ester salts with higher efficiencies than those of di- and tetra-amine macrocycles **6** and **8**. Examination of a CPK molecular model of the 18-membered polyamine **10** · primary ammonium cation complex indicated that the primary ammonium guest cation is tightly complexed with the 18-membered polyamine macrocycle *via* three hydrogen bonds between the host ring nitrogen and guest ammonium hydrogen atoms. Although tetra-amine and tetra-amide macrocycles **8** and **9** effectively transported some amino acid derivatives, ammonium cations may be loosely bound to these macrocycles *via* one or two hydrogen bonds. These results provide the further possibility that macrocycles having larger ring-sizes and suitable binding sites would show characteristic cation-binding and transport abilities for guanidinium, imidazolium, and other biological organic cations.[14]

4.3. *Armed Crown Ethers as "Podandocoronand" Type Ionophores*

The "Podandocoronand" is a new class of macrocyclic host molecule which is characterized by a monocyclic ligand skeleton and a cation-ligating donor arm group. Gokel, Okahara, and other investigators prepared a variety of crown ether derivatives of this type, and called them "lariat ethers".[15,16] They form three dimensional inclusion complexes with several alkali metal cations of intermediate stabilities between those of parent crown ethers and of corresponding bicyclic cryptands. Some of them were successfully applied to the phase-transfer process of inorganic salts, and showed characteristic chemical functionalities.

Tsukube first reported cation transport properties of some double armed crown ethers (Figure 8).[17,18] Since their parent diazo-crown ether rings strongly bind Ag^+, K^+, and other alkali metal cations, furan or thiophene arm moieties introduced are expected to act as additional ligating donors which should modify the original



	n	D
15	1	
16	2	
17	3	
18	2	
19*	2	$-CH_2OCH_2CH_2OCH_2-$

*Cryptand[2.2.2]

FIGURE 8

cation-binding and transport functionalities. When an armed crown ether forms a host-guest complex, the guest cation is enclosed in such a way that the additional donor groups on the flexible arms further coordinate the guest cation trapped in the parent crown ring.[19] The three dimensional structures of their complexes are closely similar to those of bicyclic cryptand type complexes, but the high mobility of the ligating arms attached to the macroring may permit stable but dynamic complexation.[20] Hence, this class of armed crown ethers are potential candidates for specific ionophores of several cationic guest species.

Liquid-liquid extraction experiments revealed characteristic cation-binding properties of the armed crown ethers.[17,18] Introduction of cation-ligating donor arms to a diaza-crown ring significantly modified the cation-extraction properties. For example, double armed crown ether **16** bearing furan-oxygen atoms extracted K^+, Ag^+, and Pb^{2+} ions more effectively than the corresponding parent crown ether **6**, indicating that the furan-oxygen atoms of the crown ether essentially promoted the cation-binding and extraction processes. Its extraction efficiences for Ag^+ and Pb^{2+} ions were also higher than those of bicyclic cryptand **19**, while Na^+, K^+, and NH_4^+ cations were much more efficiently extracted by cryptand **19**. These extraction results demonstrated that with some guest cations the double armed crown ether **16** formed lipophilic complexes of "intermediate" stabilities between those of parent crown ether **6** and the corresponding cryptand **19**. Several investigators have reported similar enhanced cation-binding and extraction abilities with single armed crown ether systems.[15,16] On the other hand, the double armed crown ether **18** bearing thiophene-sulfur atoms showed lower extraction ability for Ag^+ ion than parent crown ether **6**. Since it extracted K^+ and Pb^{2+} ions with efficiencies comparable to those of the crown ether **6**, the nature of the ligating donor arms markedly influenced extraction selectivity as well as efficiency.

Cation-binding selectivity of the double armed crown ether clearly depended on the size of the parent crown ether ring. Crown ethers **6**, **16**, and **18** having an 18-membered diaza-crown ring bound K^+, Ag^+, and Pb^{2+} ions more strongly than Na^+, Ba^{2+}, and Cs^+ ions. Since crown ethers **15** and **17** exhibited excellent extractabilites for guest cations which fit their parent crown rings, the appropriate combination of parent crown ring and ligating donor arm group makes it possible to design a potential host molecule specific for a lanthanoid metal and other guest cations.

Double armed crown ethers **16** and **18** showed highly enhanced cation transport abilities, compared with the corresponding crown ether **6** and cryptand **19** (Table II).[17,18] Crown ether **16** bearing furan-oxygen atoms mediated transport of K^+, Ba^{2+}, NH_4^+, and Pb^{2+} ions effectively, while other alkali and alkaline earth cations were only slightly transported. As its transport efficiencies were much higher than those of crown ether **6**, introduction of ligating furan-arms significantly increased cation transport. The cation transport profile was almost parallel to that observed in the cation extraction experiments, and cation-binding and extraction processes at the interface of Aq. I/Membrane (Figure 3) seemed to be the rate-determining step of this transport system. Thiophene-bearing crown ether **18** was an excellent ionophore for the Pb^{2+} ion. The replacement of furan-oxygen atoms in crown ether **16** by thiophene-sulfur atoms in crown ether **18** decreased transport rates for K^+ and Ba^{2+} ions, but increased that of Pb^{2+} ion. The nature of the cation-ligating arm groups effectively reflected on cation-binding and transport properties of armed crown ether compounds.

Cation transport selectivities of furan-bearing crown ethers also depended on the ring-size of their parent crown ring systems (Figure 9).[21] The crown ether **15** with a

TABLE II
Cation Transport Properties of "Double Armed Crown Ethers"

Salt	Relative Transport Rate[a]			
	6	**16**	**18**	**19**
$LiClO_4$	0.3	0.3	0.3	0.84
$NaClO_4$	0.3	0.78	0.3	6.54
$KClO_4$	0.97	7.52	2.59	1.21
$AgClO_4$	1.82	1.68	b	2.02
NH_4ClO_4	1.23	4.93	1.67	2.04
$CsClO_4$	0.33	0.92	0.56	1.42
$Ca(ClO_4)_2$	0.30	0.30	0.30	0.75
$Sr(ClO_4)_2$	0.30	1.37	0.32	2.85
$Ba(ClO_4)_2$	0.53	12.50	1.86	7.33
$Pb(ClO_4)_2$	9.09	8.17	16.00	1.63

[a]Initial transport rates of ClO_4^- anion were indicated.
[b]Ag(0) was deposited on the wall of transport experimental cell.

15-membered ring effectively mediated Na^+ ion transport, while the 21-membered crown ether **17** transported K^+ and Cs^+ ions with high efficiencies. Therefore, our new double armed crown ethers have the great advantage of "tunable" guest-binding and transport abilities. Since their guest selectivities were mainly determined by two factors, cavity size of the parent crown ring and the nature of ligating donor arm groups, it is easy to design an effective and specific ionophore of this type, which complexes with a desired guest cation with moderate stability.

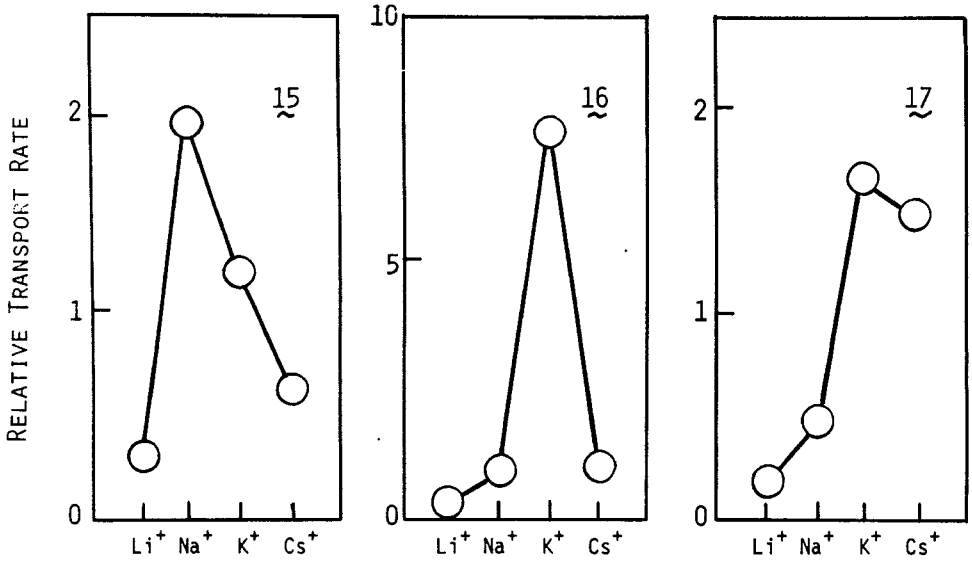


FIGURE 9 Cation transport profiles of furan-bearing double armed crown ethers having various ring-sizes.

4.4. *Armed Thia-Macrocycles and Aza-Macrocycles As "Hetero-Podandocoronand" Type Ionophores*

As a new series of "armed macrocycles" **20** and **22**, derived from thia- and aza-macrocyclic ligand molecules, were synthesized (Figure 10).[22,23] Since sulfur and nitrogen donor atoms favour heavy and soft transition metal cations in coordination,[7] these armed macrocycles are expected to form three dimensional complexes with a new series of guest cations. Furthermore, armed aza-macrocycle **22** has interesting structural features. Its macrocyclic ring-nitrogen atoms can act as potential binding sites for hydrogen bonds as well as metal coordination, and, in addition, four flexible ligating arms may accommodate a unique ordered molecular cavity as observed with some polypodand type host molecules.[24] Hence, cooperative action of polyamine ring nitrogen and furan-oxygen atoms of the armed aza-macrocycle would lead to characteristic host-guest complexations and concomitant chemical functionalities.

Armed thia-macrocycles **20** and **21** specifically formed lipophilic complexes with Ag^+ ion and solubilized it into $CHCl_3$, while other cations having similar ion-sizes were hardly extracted. The cation-coordinating properties of macroring sulfur atoms seemed to offer highly selective extraction phenomena. Modification of side-arm groups of thia-macrocycle greatly influenced the extraction efficiency, though extraction selectivity was not changed. Indeed, thiophene-bearing thia-macrocycle **20** showed moderate but highly selective extractability of Ag^+ ion, compared with phenyl-substituted ionophore **21**. Since a similarly low extraction efficiency of Ag^+ ion was observed with double armed crown ether systems, sulfur atoms of the sterically bulky thiophene ring may be ineffective donor sites for Ag^+ ion.

Armed aza-macrocycle **22** bearing furan-oxygen atoms showed unique extraction abilities, specially for NH_4^+ ion.[18] Nitrogen donor atoms of the parent aza-macrocyclic ring favoured complexations with Ag^+ znd Pb^{2+} ions, but these metal ions were precipitated and hardly extracted in the presence of aza-macrocycle **22**. In a marked contrast, it extracted NH_4^+ ion more effectively than the parent aza-

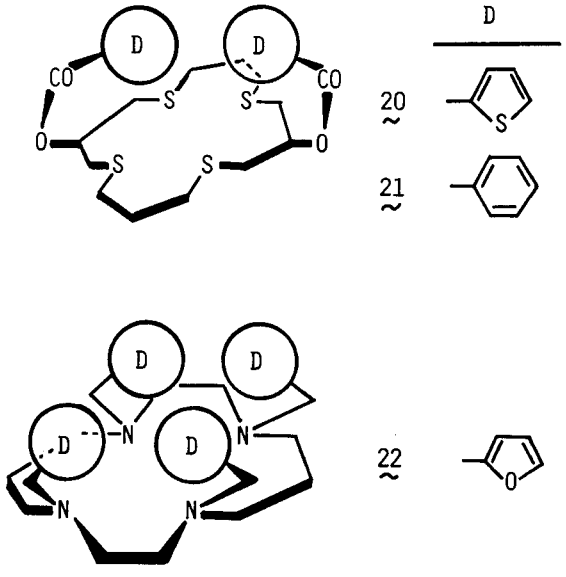


FIGURE 10

macrocycle **8**. Although its extraction efficiency was not so high, introduction of furan-arm groups into the aza-macrocyclic system clearly enhanced the extraction ability of NH_4^+ ion.

These characteristics of hetero-macrocyclic host molecules led to highly specific cation transport properties. Armed thia-macrocycle **20** transported Ag^+ ion effectively, though K^+, Pb^{2+}, NH_4^+, and other cations were hardly moved under the employed conditions.[22] Since the parent thia-macrocycle **21** exhibited a parallel transport profile to the armed thia-macrocycle **20**, macrocyclic sulfur atoms played important roles in selective extraction and transport of Ag^+ ion. As pointed out in the double armed crown ether systems (Table II), attachment of thiophene-arms to the macrocyclic ring system decreased extraction ability but increased transport efficiency of Ag^+ ion. Probably, armed thia-macrocycle **20** formed a Ag^+ ion complex of moderate stability which is required for effective cation transport.

Armed aza-macrocycle **22** specifically discriminated NH_4^+ ion from K^+ and other guest cations in the transport process.[23] It realized highly effective transport of NH_4^+ ion, while H^+, K^+, and other alkali and alkaline metal cations were hardly transported. Since parent aza-macrocycle **8** exhibited a low transport rate of NH_4^+ ion, the cooperative action of furan-oxygen and macrocyclic ring-nitrogen atoms must be essential for promoting specific transport. Details of the transport mechanism are not clear, but NH_4^+ ion may be distinguished from K^+ ion not by "ion size" (NH_4^+: 2.89 Å; K^+: 2.66 Å) but by "charge distribution" (NH_4^+: tetrahedral; K^+: spherical). A CPK molecular model of the armed aza-macrocycle **22** · NH_4^+ cation complex afforded the prediction that the guest NH_4^+ ion would be wrapped "tetrahedrally", donating two hydrogen bonds to two diametric ring nitrogen atoms as well as to two furan-oxygen atoms. A similar molecular cavity for tetrahedral guest-binding has been reported in 1,4,7,10-tetrakis(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane system.[25] Such a tetrahedral geometry for binding of NH_4^+ cation could not be constructed by double armed crown ethers such as **16**. Three dimensional arrangement of donor sites is an essential requirement for precise shape-recognition of guest cation.

In this article, we presented several kinds of armed macrocyclic host molecules, which were considered as new ionophores capable of specific cation recognition. Their chemical functionalities were demonstrated to be effectively controlled by appropriate combinations of their ligand components. Ring-size and donor atoms of the parent macrocyclic ligand, number and nature of arm donor group, and three dimensional molecular geometry are important and variable factors in the molecular design of a specific ionophore. Since we know many kinds of macrocyclic host molecules, further extensions along this line may develop new and excellent host and ionophore molecules for a given guest species.

4.5. *Acyclic Crown Ethers as New "Podand" Type Ionophores*

Recently several functionalized "acyclic" crown ethers, "podands", have been designed by modelling biological acyclic ionophores such as monensin and lasalocid A.[26] They are characterized by formation of pseudo-cavities, in which ether-oxygen atoms are suitably arranged for specific cation-ligation. Spectroscopic studies of their metal complexes revealed that chain ends of the acyclic ionophore are linked by intramolecular interactions and the guest cation is located at the center of the pseudo-cavity as in the case of the metal complex of a macrocyclic ionophore. Although most of synthetic acyclic ionophores showed lower cation-binding abilities than corresponding

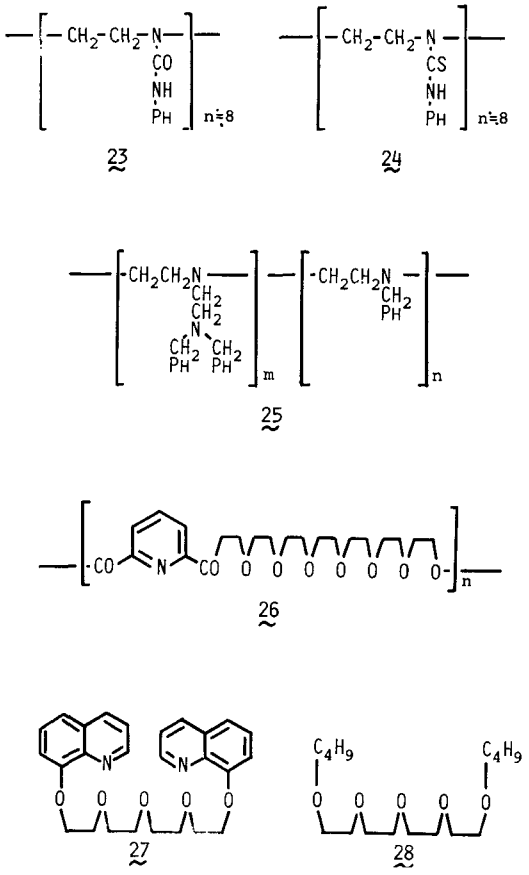


FIGURE 11

macrocyclic analogues, they offer advantages of facile synthesis, versatility in molecular structure, and simple complexation kinetics.

Tsukube *et al.* developed several neutral podand type ionophores showing excellent cation-recognition and transport functionalities (Figure 11). Urea- and thiourea-bearing octa-amine derivatives **23** and **24**, so-called "urea oligomers", specifically mediated transport of Cu^{2+} ion.[27,28] Lipophilic polyethylenimine derivative **25** transported Zn^{2+} ion more effectively than Cu^{2+}, Co^{2+}, and Ni^{2+} ions.[29] Pyridine-bearing polyether **26** was a potential ionophore for various organic cations.[30] Among the synthetic acyclic ionophores presented, quinoline-bearing acyclic crown ether **27** is of particular interest.[31,32] It provides several adequate chemical properties as a potential podand type ionophore for bioactive catecholamines and related cationic guest species:

(i) Its terminal quinoline groups act as powerful hydrogen bonding sites for guest ammonium cations;

(ii) The quinoline groups also function as anchoring points with locally fixed donor sites on which guest cation can take hold;

(iii) The flexible nature of the acyclic ligand may permit dynamic conformational changes in the binding and releasing processes.

Thermodynamic and kinetic studies demonstrated that this type of acyclic crown ethers were somewhat weak cation-binding ligands, but their dynamic cation-binding and releasing properties may be suitable for efficient ionophores.[31]

Quinoline-bearing acyclic crown ether **27** was shown to be an excellent ionophore, especially for some organic ammonium cations (Table III).[32] Interestingly, it effectively discriminated organic ammonium cations from K^+, Na^+, NH_4^+, and other inorganic cations in transport processes. Since butyl-bearing acyclic crown ether **28**, having polyether linkages, hardly transported ammonium and other metal cations, quinoline-terminal groups of the ionophore **27** acted as effective binding sites of ammonium cations. Probably, cation coordination of quinoline nitrogen atoms induces pseudo-cyclic conformation of the acyclic ionophore and successive binding of polyether sequence. A similar cooperative cation-binding has been observed in pyridine-bearing polymer ionophore **26**.[30]

Hiratani, Simon, and other investigators have also prepared a wide variety of acyclic ionophores showing interesting chemical functionalities,[33-35] and some of them were successfully applied to ion selective electrodes.

TABLE III
Cation transport properties of podand type ionophores

Salt	Relative transport rate		
	1	**27**	**28**
$KClO_4$	28.5	0.9	0.2
NH_4ClO_4	8.6	3.0	0.2
$C_6H_5CH_2CH_2NH_3ClO_4$	12.9	12.5	1.2
$C_6H_5CH_2C(CH_3)(CH_3)NH_3ClO_4$ (phentermine)	18.5	17.1	0.1
$C_6H_5CH(OH)CH(CH_3)NH_3ClO_4$ (nonrephedrine)	6.9	6.2	0.5
$(CH_3O)_2C_6H_3CH_2NH_3ClO_4$ (homoveratrylamine)	14.1	12.7	1.0

4.6. *Anion-Bearing Ionophores with Cation Transport Functionalities*

Anion-bearing ionophores showed cation transport properties largely different from the neutral ionophores. As a representative example, the monensin-mediated biological transport system is illustrated in Figure 12A.[36] Monensin **4** has cation-ligating ether linkages and a terminal carboxylic acid moiety, and acts as a pseudo-cyclic ionophore *via* intramolecular hydrogen bonding between terminal carboxylate and suitably placed –OH group. The guest cation is strongly bound to the terminal carboxylate anion and several ether-oxygen atoms, and then the complex penetrates through the membrane. In biological transport, dissociation of the terminal carboxylic acid moiety is specifically coupled with its cation-binding and releasing processes, and guest Na^+ ion is effectively transported with the aid of H^+ gradient.

Apart from biological transport system, Tsukube *et al.* developed new biomimetic membrane transport (Figure 12B), in which monensin **4** and related biological

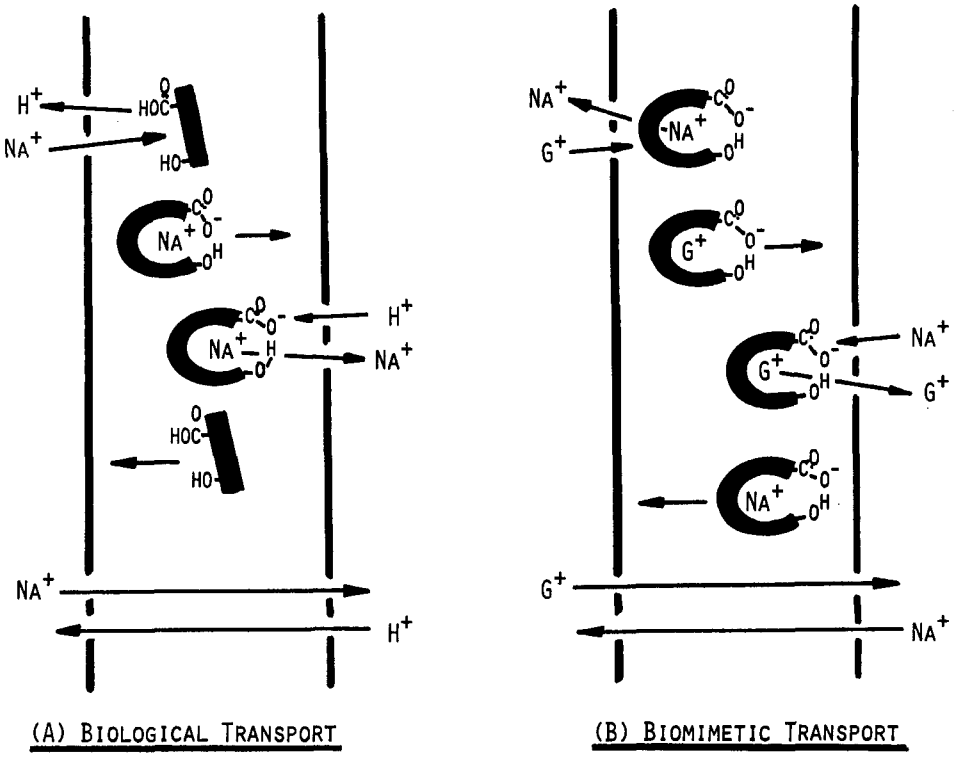


FIGURE 12 Cation membrane transport systems mediated by anion-bearing ionophores monensin and lasalocid A: (A) biological transport and (B) biomimetic transport.

Na^+: sodium cation; H^+: proton; G^+: guest cation.

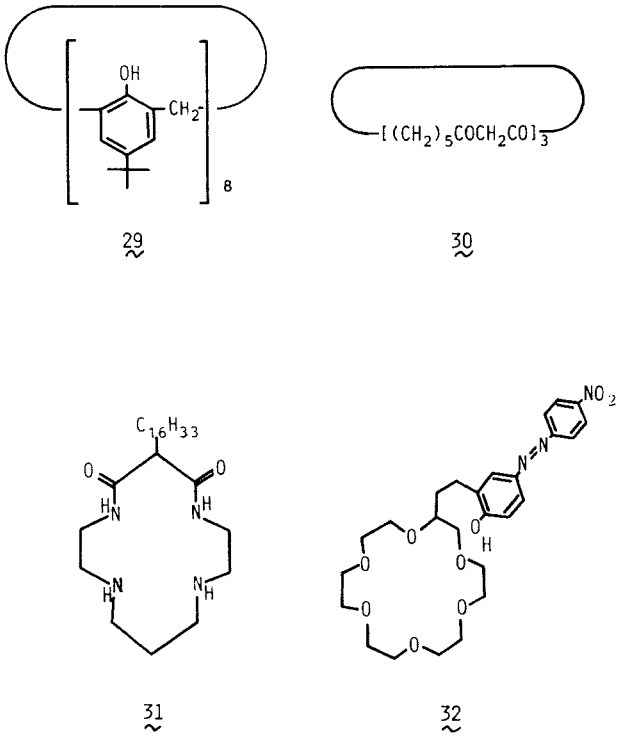
ionophores effectively transported amino acid ester salts and other metal cations in an unnatural manner.[37] Although the present transport system is of no direct biological significance, it clearly demonstrated new and useful transport functionalities of anion-bearing ionophores.

Monensin **4** effectively transported several amino acid ester salts, Ag^+, and Pb^{2+} ions *via* a cation/cation exchange mechanism (Figure 12B), while Cu^{2+}, Ni^{2+}, and other transition metal cations were hardly transported. Its transport selectivities were apparently controlled by the "cation-cavity size concept" familiar in crown ether chemistry.[7] A CPK molecular model strongly suggested that the pseudo-cavity of monensin is composed of an approximately 17-membered ring with six oxygen donor atoms. This meets with the sizes of effectively transported ammonium, Ag^+, and Pb^{2+} ions. In a marked contrast, Cu^{2+}, Ni^{2+}, and other transition metal cations seem to be too small to interact effectively with oxygen donor atoms and are hardly transported by the monensin. The nature of the antiport cation largely influences overall transport rates, and the Na^+ cation was found to be the most effective among alkali metal cations. Since monensin is known to bind Na^+ ion very tightly,[36] it effectively accelerated the cation exchange process at the interface of Membrane/Aq. II.

Lasalocid A **5**, also a typical anion-bearing biological ionophore,[38] exhibited interesting transport properties for guest cations. It offered high transport rates of Ag^+, Ni^{2+}, Zn^{2+}, and Co^{2+} ions, though amino acid transport was slightly mediated.

Its transport profile was markedly different from that observed with monensin, and the molecular structure of the employed ionophore was an essential factor in determining the transport profile. Although the stoichiometry and structure of the complex are somewhat complicated,[39,40] the salicylic acid moiety of the lasalocid A may play a crucial role in the binding and transport of these metal cations.

Synthetic anion-bearing ionophores have been recently investigated. Izatt *et al.* employed cyclic oligophenol **29**, "calixarene", and revealed its effective transport ability for Cs^+ ion.[41,42] Tabushi *et al.* synthesized macrocyclic host molecules such as **30** bearing β-diketone moieties and used them as practical extraction reagents for uranyl ion.[43,44] Kimura *et al.* developed selective membrane transport of Cu^{2+} ion, in which dioxo-cyclam derivative **31** acted as a specific anion-bearing ionophore.[45] A variety of anion-capped crown ethers including **32** have also been presented.[46,47] Some of them are summarized in Figure 13.



29 30 31 32

FIGURE 13

5. SYNTHETIC IONOPHORES SHOWING ANION-BINDING AND TRANSPORT FUNCTIONALITIES

5.1. *Membrane System for Anion Transport*

In contrast to a large variety of synthetic cation transport ionophores, we know only limited examples of synthetic "anion transport ionophores". Thus, it appears highly desirable to search for a new class of ionophores which would display excellent

transport abilities for amino acids, nucleic acids, and other anionic guest species. Like the cation transport ionophores, new and effective anion transport ionophores should offer exciting developments in organic, inorganic, and biological chemistry.

Anion transport is mediated, in principle, by synthetic ionophores which possess appropriate anion-binding sites and suitable hydrophobic portions. There are two basic types of membrane transport for anionic guest species: antiport and symport (Figure 14). In the antiport transport system, a lipophilic cation (ionophore) binds the guest anion *via* exchange of coordinated anion at the interface of Aq. I/Membrane and carries it through the Membrane. Then the coordinated guest anion is exchanged again by the antiport anion and released into the Aq. II phase. Hence, the net result is that the guest anion and antiport anion are transported in the opposite directions. 'Symport' transport system is consisting of somewhat different elemental processes. The guest anion and symport cation are complexed with a common neutral ligand (ionophore) which is solubilized in the Membrane phase. After the complex diffuses across the Membrane, it decays into the original ligand and into the original ion-pair at the other interface of the Membrane. Hence, guest anion and symport cation are transported in the same direction.

Lehn *et al.* presented a typical antiport transport system in which lipophilic quarternary ammonium cations such as trioctylmethyl ammonium chloride **33** formed

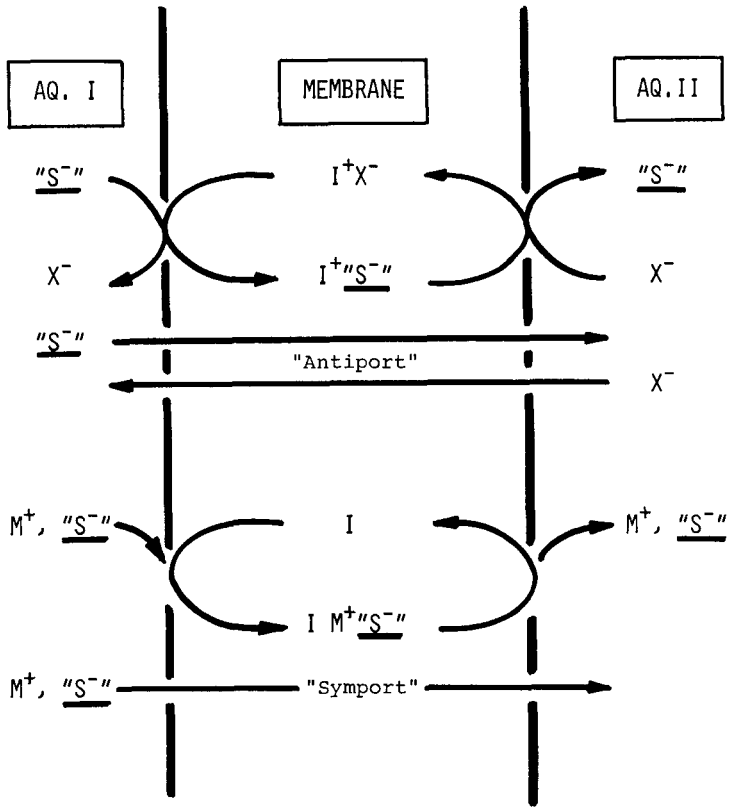


FIGURE 14 Two typical membrane systems for anion transport: "Antiport" and "Symport". I or I^+: Ionophore; S^-: guest anion; X^-: antiport anion; M^+: symport cation.

ion-pair complexes with amimo acid anions and transported them.[48] Tabushi *et al.* designed a diammonium cation-surfactant and successfully applied it to the selective transport of the ADP anion.[49] In these transport systems, the nature of quarternary ammonium cation ionophore and antiport anion largely influenced on the anion transport profiles.

Tsukube designed new synthetic anion transport ionophores by considering (i) size of guest and ionophore; (ii) nature of the anion-binding force; and (iii) their anion coordination geometries. As a new class of anion-binding sites, we chose macrocyclic polyammonium, alkali, and transition metal cations. Macrocyclic polyammonium cations, multi-protonated polyamine macrocycles, are known to show unique anion-binding properties, depending on the size and shape of the macrocyclic polyamine skeleton.[50] Metal complexes are expected to recognize and bind the guest anions *via* "ligand-metal ion-guest anion" ternary complexations. Therefore, introduction of these characteristic anion-binding sites into the lipophilic ionophores might provide new and excellent anion-binding and transport functionalities, which were not attained with simple ammonium cation ionophores.

5.2. *Polyammonium Macrocycles as Synthetic Ionophores of Anionic Guests*

Tsukube investigated anion-binding and transport properties of a series of lipophilic polyammonium macrocycles.[51,52] Liquid-liquid extraction experiments revealed that picrate and other guest anions were effectively extracted *via* interactions with protonated polyamine macrocycles (see Figure 6), and that the extracted amounts of guest anions largely depended on the ring-size of the polyamine compound and the pH value of aqueous phase. Typically, 14-membered tetra-amine macrocycle **8** picked up picrate anion more effectively from the acidic aqueous solution than from the neutral solution, while trioctylmethyl ammonium chloride surfactant **33** showed pH-independent extraction properties. Although protonation of lipophilic polyamine macrocycles was somewhat suppressed in liquid-liquid extraction reaction systems, the resulting macrocyclic polyammonium cations acted as effective anion binders. An anion transport membrane was constructed by using polyammonium macrocyclic ionophores (Figure 15). After being protonated at the interface of Aq. I/Membrane, the polyamine macrocycle (protonated form) binds anionic guest and carries it through the Membrane. At the Membrane/Aq. II interface, the guest anion is released into the Aq. II phase, coupled with deprotonation of polyamine macrocycle or with anion exchange. Hence, the concentration gradient of proton or antiport anion drives the anion transport. As guest anions, we chose a series of biological amino acid and some polycarboxylate anions, and typical transport results are summarized in Table IV.[52]

Polyammonium macrocycles derived from **6**, **8**, and **10** were pH-responsive ionophores of Z-amino acid derivative anions, whereas corresponding polyamides **7**, **9**, and **11** hardly transported guest anions. Their transport rates for Z-amino acid anions were dependent upon the pH values of the Aq. I phase, i.e., the transport rates decreased with increasing pH values. On the other hand, surfactant ionophore **33** exhibited constantly high transport rates at a wide range of pH values. These transport behaviours of polyamine macrocycles were almost identical with those of the extraction experiments, indicating that the present transport process was coupled with interfacial protonation of polyamine macrocycles, and essentially regulated by the proton gradient across the membrane.

By choosing antiport anions, anion transport properties of polyammonium macrocycles could be controlled: Cl^- and AcO^- anions were found to offer higher transport rates than OH^- and SO_4^{2-} anions. Since no diffusion was detected in the

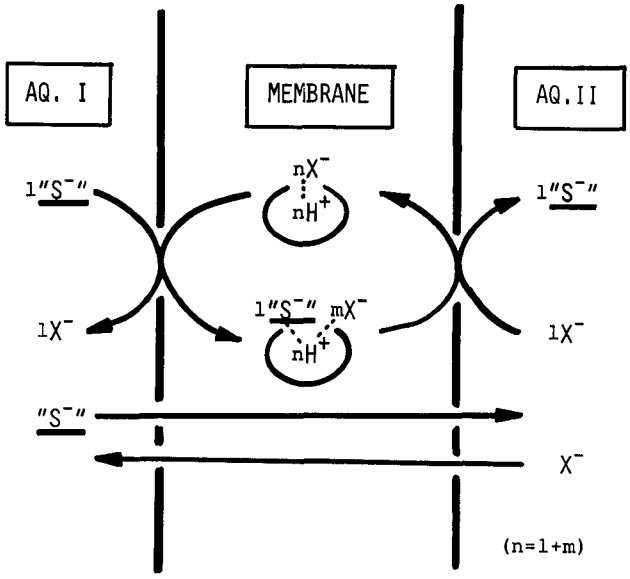


FIGURE 15 Anion transport membrane mediated by polyammonium macrocycle.

S^-: guest anion; X^-: aniport anion; H^+: proton; l, m, and n: numbers of anion and proton.

absence of the antiport anion, it is clear that effective transport is driven by the antiport gradient. Similar effects of antiport anions were confirmed in quarternary ammonium cation **33** system, and the same factors may control the anion-releasing processes in both cases.

Polyammonium macrocyclic ionophores showed great advantages for the transport of dicarboxylate guest anions. They transported dicarboxylic Z-glutamic acid and

TABLE IV
Anion transport properties of polyammonium macrocyclic ionophores

Guest Anion[a]	Antiport Anion	Relative transport rate				
		6	**8**	**9**	**10**	**33**
Z-Gly(pH 4.50)	None		0			0
	AcO^-, 0.5M		1.21			4.12
	OH^-, 0.5M		0.19			0.68
	Cl^-, 0.3M		0.86			2.78
	Cl^-, 0.5M	0.91	1.17	0	0.71	2.93
(pH 5.29)	Cl^-, 0.5M		0.57			3.21
(pH 6.98)	Cl^-, 0.5M		0.14			3.30
Z-Ala(pH 4.34)	Cl^-, 0.5M	0.84	1.28	0	0.66	3.45
Z-Val(pH 4.68)	Cl^-, 0.5M	0.52	0.50	0	0.45	1.79
Z-Gln(pH 4.50)	Cl^-, 0.5M	0.56	1.96	0	1.57	7.31
Z-Glu(pH 4.55)	Cl^-, 0.5M		2.76	0.10	1.63	1.62
Z-Asn(pH 4.54)	Cl^-, 0.5M	0.53	2.69	0.09	1.70	9.54
Z-Asp(pH 4.60)	Cl^-, 0.5M		2.58	0.41	2.56	19.3

[a]The values shown in parentheses were pH values of Aq.I adjusted initially.

Z-aspartic acid anions with efficiencies comparable those of corresponding monocarboxylic Z-glutamine and Z-asparagine anions. In a marked contrast, the quarternary ammonium cation **33** transported monocarboxylate anions much more effectively than dicarboxylate anions. Although pKa values of the polyamine macrocycles and guest carboxylic acids should be largely shifted in the non-polar membrane phase and at the interface of the membrane/aqueous phase, dicarboxylate anions may effectively associate by ionic hydrogen bonds with polyamine protons in the macrocyclic cavities. Lehn *et al.* and Kimura *et al.* have proposed similar hydrogen bonding schemes between simple polyamine macrocycles and polyanion guests in homogeneous aqueous solution.[53,54]

Table V emphasizes structural complementarity between polyammonium type ionophore and guest anion for the polyanion transport system. For benzenedicarboxylic acids, polyammonium macrocycles transported the o-isomer much more effectively than the m- and p-isomers. Similarly, they favoured smaller anions of benzene-1,2,3- and 1,2,4-tricarboxylic acids rather than larger anion of benzene-1,3,5-tricarboxylic acid. Thus, the polyanions which were effectively transported with polyammonium macrocycles were the smaller and were highly charged ones. The ring-size of polyammonium macrocycle also influenced the polyanion transport ability: the 18-membered hexa-amine **10** transported the larger pyromellitic acid anion more effectively than the 14-membered tetra-amine **8**, while compound **10** showed lower transport rates for smaller di- and tri-carboxylic acid anions. Under the same conditions, quarternary ammonium cation ionophore **33** showed non-selective transport abilities for these polyanionic guest species.

In biological transport processes, dicarboxylate anions are transported by several complicated carrier proteins.[55] Although the chemical aspects of anion recognition and transport mechanisms are as yet unclear, the present results strongly suggest that polyamine macrocycles may serve as simple and primitive chemical models of the several carrier proteins having amine residues such as lysine. Therefore, further

TABLE V
Transport of polyanions by polyammonium macrocyclic ionophores

Guest Anion	Relative transport rate				
	6	**8**	**9**	**10**	**33**
Benzenedicarboxylic acid (pH = 5.42)[a]					
1,2-	1.15	2.30	0	1.60	1.47
1,3-	0	0.07	0	0.07	2.70
1,4-	0.09	0.18	0.04	0.14	2.09
Benzenetricarboxylic acid (pH = 4.70)[a]					
1,2,3-	0.50	4.18	0.04	0.14	4.47
1,2,4-	0.29	3.17	0.04	1.57	5.16
1,3,5-	0.03	0.16	0	0.11	1.39
Benzenetetracarboxylic acid (pH = 4.70)[a]					
1,2,4,5-	0.15	1.71	0.08	5.43	4.78

[a]The values shown in parentheses were pH values of Aq.I adjusted initially.

modification of ring-size and shape of polyammonium macrocycle may offer new possibilities in the design of highly specific membranes for practical use as well as in modelling biomembrane transport systems.

5.3. *Lipophilic Transition Metal Complexes as Synthetic Ionophores of Anionic Guests*

Incorporation of positively charged metal center into the synthetic ionophore offered novel development of specific host and ionophore molecules for anionic guest species. We chose certain lipophilic transition metal complexes as new anion transport ionophores, "metallo-carriers". For example, transition metal ions coordinated by 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane **34**, so-called tbcyclen (Figure 16), showed effective anion transport properties.[56] Their noteworthy features are:

(i) The macrocyclic polyamine ligand skeleton is prepared and modified without difficulty.

(ii) A number of transition metal ions such as copper, nickel, and cobalt ions are placed in the cavity of the polyamine ligand.

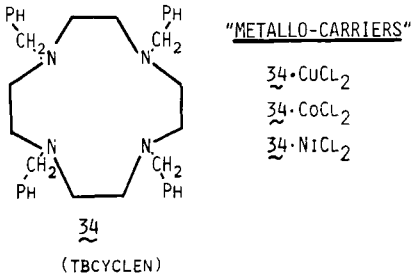
(iii) Anion-binding properties are significantly controlled by a combination of polyamine ligand and coordinated metal ion.

(iv) The substituents of the polyamine ring should create a hydrophobic micro-environment around the central metal ion, displaying a good balance of hydrophobicity and hydrophilicity.

Naturally occurring metallo-enzymes recognize and bind the anionic substrates *via* "ligand protein-central metal cation-guest anion" type complexation. Similar anion-recognition and binding properties are expected to be realized in the simple transition metal complexes.[57] Indeed, tbcyclen-$CuCl_2$, $-NiCl_2$, and $-CoCl_2$ complexes showed excellent extraction abilities for a series of amino acid derivative anions. In particular, phenylalanine, leucine, and other hydrophobic anions were more effectively extracted than hydrophilic alanine and glycine derivatives. Since their structural features are markedly different from those of ammonium cation type ionophores such as **33**, these "metallo-carriers" should give rise to new transport functionalities for guest anions.

Expectedly, tbcyclen-transition metal complexes effectively mediated artificial active transport of amino acid, dipeptide, and tripeptide derivatives *via* the antiport

$[C_8H_{17}]_3N^+CH_3 \cdot CL^-$ 33



34
(TBCYCLEN)

"METALLO-CARRIERS"

34·$CuCL_2$
34·$CoCL_2$
34·$NiCL_2$

FIGURE 16

TABLE VI
Anion transport properties of metallo-carrier (active transport of Bz-amino acid anions)

Ionophore	Guest Anion	Antiport Anion	Equilibrated Guest Concentration Ratio[a]
34·$CuCl_2$	Bz-Gly	None	1.00
		Cl^-	2.54
	Bz-Ala	Cl^-	7.67
	Bz-Val	Cl^-	3.38
	Bz-Leu	Cl^-	2.30
	Bz-Phe	Cl^-	1.30
33	Bz-Gly	Cl^-	4.99
	Bz-Ala	Cl^-	6.23
	Bz-Val	Cl^-	3.09
	Bz-Leu	Cl^-	1.73
	Bz-Phe	Cl^-	1.14

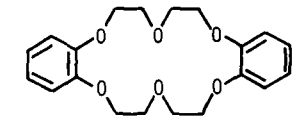
[a][Guest Anion in Aq.II]/[Guest Anion in Aq.I]. Initial value, 1.00

mechanism. As shown in Table VI, tbcyclen-$CuCl_2$ effectively transported several Bz-amino acid derivative anions against their concentration gradients. Particularly, Bz-Ala was much more effectively transported than other amino acid anions examined: Bz-Ala > Bz-Val > Bz-Gly > Bz-Leu > Bz-Phe. Their transport selectivities and efficiencies were easily modified by changing the central metal atom: the copper complex effectively transported Bz-Ala; the nickel complex favoured Bz-Glu; and the cobalt-containing complex carried Bz-Gly at a higher rate. Although these metallo-carriers have closely similar metal coordination geometries, the anion-coordinating ability of the central metal cation might attain these characteristic transport properties. Other transport experiments showed that Cl^- anion was a more effective antiport anion than ClO_4^- and SCN^- anions, possibly being more easily exchanged by amino acid anions at the interface and thus giving rise to higher transport rates. When the antiport anion was Cl^-, the concentration ratio of Bz-Ala anions across the membrane increased from an initial value of 1 to ca. 8 after 24 h. Since their transport abilities were more selective and efficient than those displayed by ammonium cation ionophore **33**, metallo-carriers were recognized as a new class of anion transport ionophores.

Lipophilic bathophenanthroline, trioctylamine, cyanocobalamine, and other neutral multidentate ligands were demonstrated to form potential metallo-carriers for anionic guest species.[58,59] Various combinations of lipophilic ligand and central metal cation would provide interesting and varied anion transport phenomena.

5.4. *Lipophilic Alkali Metal Complexes as Synthetic Ionophores of Anionic Guests*

Lipophilic alkali metal complexes, composed of crown ethers and related macrocycles, effectively transported anionic guest species *via* the symport mechanism (Figure 14). Although crown ethers have been well-recognized as model ionophores for selective transport o alkali metal cations, the rates of cation transport have largely been influenced by the nature of anionic species which accompanied the cation·crown ether complex. Lamb *et al.* presented systematic studies on this problem,[60] and proposed the possibility that anionic species could be selectively transported by crown ethers. Then, we tested some kinds of crown ethers, acyclic crown ethers, and cryptand compounds as anion transport ionophores (Figure 17). In some biological transport



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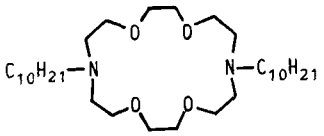

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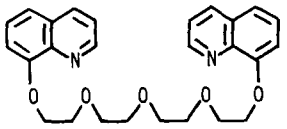

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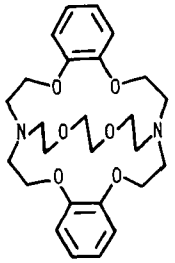

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FIGURE 17

systems, amino acid and sugar derivatives are believed to be carried with cations such as Na^+ and K^+ by a common ionophore *via* so-called "Mitchell's symport".[61] By using macrocyclic host molecules, cation-dependent amino acid symport could be artificially realized.

Several crown ether compounds mediated symport transport of amino acid derivative anions and alkali metal cations with high efficiencies (Table VII).[62-64] When dibenzo-18-crown-6 **1** was typically employed, the transport rate of the Bz-Phe anion depended on the nature and concentration of the symport metal cation: K^+ ion was more effective in promoting amino acid anion transport than Na^+ and Cs^+ ions; an increase in the K^+ ion concentration in the Aq. I phase resulted in a highly enhanced transport rate. These transport properties paralleled those of cation extraction experiments with the same crown ethers, and suggested that coupling to the K^+ ion gradient was used to pump up the amino acid anion.

The present symport system offered an interesting transport selectivity for the following series of amino acid derivative anions: Bz-Gly < Bz-Ala < Bz-Val < Bz-Leu < Bz-Phe. This is a reversed transport sequence from that observed with transition metal complex type ionophores. Since the amino acid derivatives with higher

TABLE VII
Anion transport properties of lipophilic alkali metal complexes

Guest anion	Symport cation	Relative transport rate			
		1	**27**	**35**	**36**
Bz-Phe	K^+	13.0	0.6	3.1	3.8
	Na^+	1.2	0.2	1.1	9.9
	Cs^+	1.9	0.2	0.4	7.0
Bz-Leu	K^+	3.4	0.1	1.6	5.5
Bz-Met	K^+	4.8	0.2	1.6	5.9
Bz-Val	K^+	2.0	0.2	1.0	5.2
Bz-Ala	K^+	0.2	0	0.7	6.6
Bz-Gly	K^+	0.1	0.1	0.8	4.0

hydrophobicities were effectively transported *via* the symport mechanism, the anion extraction into the membrane with the K^+·crown ether complex could be the rate-determining step. Other crown ethers and related multidentate ligands exhibited similar transport properties, and their transport abilities were confirmed to increase according to the following order of ionophores: cryptand **36** > crown ether **1** > aza-crown ether **35** > acyclic crown ether **27**. Since the same order was established for complexation constants between K^+ ion and each ligand, effective K^+ binding of the ligand led to fast transport of amino acid derivative anions. Here, we present two different types of "metallo-carriers", derived from transition and alkali metal cations. By choosing these metallo-carriers, selectivity, efficiency, and direction of anion transport process could be adjusted as desired.

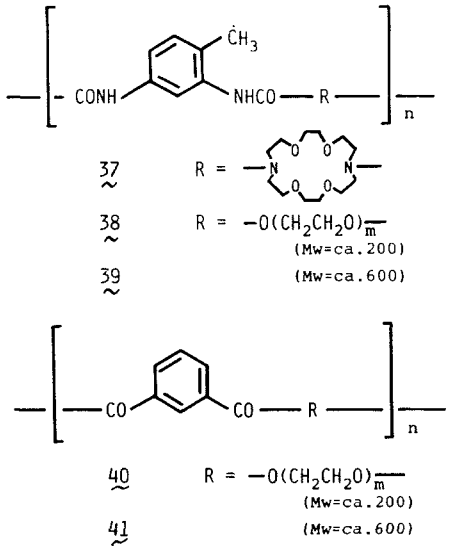

FIGURE 18

Similar anion symport was realized by using polymeric ionophores **37**–**41** (Figure 18).[65] They consisted of a $-CH_2-CH_2O-$ sequence as the cation-binding site, separated by suitable spacer groups. The acyclic polyether sequence seemed to be a weak but suitable cation binder, because the best ionophore of this type is a ligand capable of giving a moderately stable cation complex. Interestingly, linear polyether-containing polymers **38**–**41** effectively mediated transport of Z-amino acid anions, together with alkali metal cations, while corresponding crown ether polymer **37** slowly transported guest anions. Their anion transport abilities were controlled by the same factors as observed with the above-mentioned crown ether type ionophores: K^+ ion offered higher transport efficiencies than Na^+ and Cs^+ ions; the ionophore with a polyether chain long enough for cation-binding showed a high transport rate of guest anion. Recently biological ionophores such as valinomycin and nonactin were applied to the present type transport system, and optical resolution of racemic amino acid derivatives may be envisaged.

6. CONCLUDING REMARKS

We have designed a variety of synthetic ionophores capable of transporting guest ions by considering "host-guest complexation". They effectively controlled transport profiles and allowed the transport to be coupled to other chemical processes such as proton gradient.

Setting up of the cation transport membrane was made by using two different types of ionophores. Coronands and related neutral ionophores mediated cation transport, in which guest cations and symport anions were transported in the same direction. On the other hand, monensin and other anion-bearing ionophores exchanged guest and antiport cations across the membrane. Their transport profiles clearly depended on complementarity between ionophore and guest species. Alkali, alkaline earth, heavy, transition metals, and molecular cations were selectively transported by our designed ionophores.

Synthetic ionophores of anionic guest species were also successfully designed, though this area has been comparatively little explored. Newly designed ionophores, having macrocyclic polyammonium, transition, and alkali metal cations as binding sites, mediated specific transport of organic anions of biological significance such as amino acid derivatives and polycarboxylate anions.

Such biomimetic approaches in membrane transport provided the means of molecular design of effective host molecules. They also made it possible to analyze elemental steps and mechanisms of transport phenomena, to couple transport with chemical potential, energy, and signal transduction, and to mimic biological transport processes. Furthermore, there are various possible applications, for instance, in separations, purifications, and related processes.

At the present stage, we have little knowledge of natural and artificial ion-recognition and transport mechanisms, but organic chemists can greatly contribute to a variety of fields of biology and industry as well as chemistry through molecular design of new and potential host molecules. We believe that our attempt is one step toward the final goal.

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